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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/699,852	11/04/2003	Susumu Hirose	244855US0	5771

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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	**PAPER NUMBER**
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	03/15/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 03/15/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/699,852	HIROSE ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/17/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's declaration filed on 12/21/06, remarks filed on 12/06/06 and IDS filed 01/17/07 and has been acknowledged.

Claims 1-6 are pending and are examined in this office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/06/06 has been entered.

Claim Rejections - 35 USC § 103

Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Siden et al, Methods. 17(2):112-124, 1999) in view of Saffrin et al (US 4,868,311, 1989) and Chevalier et al (J Histochem. Cytochem. 45(4):481-91, 1997), for the same reasons of record as set forth in the office action mailed on 07/12/06.

Invention is drawn to a method for detecting negatively supercoiled DNA in a cell using a biotinylated psorlan probe.

Siden et al teaches use of psoralen cross-linking as probe of torsional tension and topological domain size in vivo. The cited art further teaches a protocol for measuring super-coiled DNA by treating cells with 313nm UV light and Me3-psoralen (page 116 col.2, table-1). The cited art further teaches that the binding constant intercalating agents such as psoralen and ethidium bromide are proportional to the level of negative supercoiling and there exists a linear correlation between photobinding of psoralan and negative superhelical density. The cited art further teaches that to

determine superhelical density in-vivo, measurement of psoralen binding to DNA can be achieved by quantitating the incorporation psoralan into total genomic DNA (page 113, col.2, para.2-3). The cited art further teaches measurement of topological domain size by measuring R1/N values (page 114, col.1 para. 2-3; page 122, fog-3). Even though Siden teaches use of Me3-psoralen for the quantitation of super coiled DNA the cited art does not teaches the use of biotinylated pspralen.

Saffrin et al teaches biotinlayted-psoralen (BPsor) which cross-links to DNA in the presence of UV rays (col. 9, lines 45-55). The cited art further teaches that BPsor binds covalently to DNA in a near UV photoreaction, resulting in interstrand crosslinks, and like other biotinylated molecules it binds to avidin, even after it has been incorporated into DNA. The cited art further teaches that the biotinylation does not interfere with its biological activity in lymphocytes. The cited art further teaches that the delivery of BPsor to cells as an avidin-BPsor conjugate (col. 5 lines 12-34; col.12 lines 24-68). The cited art further teaches the detection of cross-linked DNA using biotin-avidin based ELISA system (col.11 lines 23-51).

Chevalier et al provides a review for in situ hybridization (ISH) techniques using biotinylated probes. The cited art further teaches that biotin, a small vitamin molecule (M_r 244), binds with high affinity to avidin, a protein largely distributed in egg whites (M_r 70,000), which can be conjugated to different markers such as fluorescent dyes, peroxidase, ferritin, and colloidal gold (page 482, col.1 para.3). The cited are further teaches permeabilization of cells or tissue section using permeation-promoting agent (page 484, col.1 para.2; page 488, col.1 para. 4). The cited art further teaches the detection of tissue or cells containing DNA of interest using biotinylated probes (see Fig. 4-6).

Thus it would have been obvious to one ordinary skilled in the art at the time the instant invention was made to modify the invention of Siden by substituting the Me3-psoralen with biotinlayted-psoralen (BPsor) for in situ detection of DNA. One would have been motivated to do so because biotin-avidin system provides flexibility in the selection of different diagnostic labels. One would have a reasonable expectation of success, since the use of biotin-avidin system for intra cellular detection of target

moieties has been routine in the art at time the instant invention was made. Thus the invention as claimed is prima facie obvious in view of cited prior art of record.

Response to arguments and Dr. Susumu Hirose's Declaration (35 USC 103)

The applicant argues that the important feature of the claimed methods is that the negatively supercoiled DNA is detected in cells. Since the DNA is detected in the cells, the claimed methods do not require extracting the DNA from the cells in order to be analyzed. The applicant argues that although Sinden et al describes a method of measuring super-coiled DNA, that method requires electrophoretic separation and the cited art provides no evidence showing that the measurement of super-coiled DNA is possible in-vivo as well. The applicant argues that Chevalier et al describe in situ hybridization. The applicant argues that there is no descriptive of using biotinylated psoralen in that reference. The applicant argues that as compared with the cited references; the present invention provides a novel method for detecting negatively supercoiled DNA in living cells, which is characterized by visualizing negatively supercoiled DNA in living cells. The applicant argues that the metnod as calimed in the present specification makes it possible to detect any fragment of negatively supercoiled DNA, which would never have been possible to detect if its detection is carried out by a classical method using the hybridization technique. Therefore, the method of the present invention cannot be predicted whatsoever by one skilled in the art.

Dr. Susumu Hirose's declaration states that a study to discriminate between human leukemia cells and leukocytes using a biotinylated psoralen deravatives was performed which revealed the in the absence of retinoic acid, strong signals of biotinylated psoralen was detected in the nucleous of leukania cell. However, the signals be, came faint after induction of differentiation into leukocyte with refinoic acid.

However, applicant's arguments and the declaration provided are found not persuasive. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (*i.e. in living cells; see remarks and declaration*) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the

specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Furthermore, the arguments taken as a whole rely heavily on the deficiencies of each reference taken alone. One cannot show non-obviousness by attacking references individually where the rejections are based on combinations of references. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In the instant case combined teaching of Sinden et al., Saffrin et al. and Chevalier et al. clearly suggest the invention as claimed, since it obvious to one ordinary skilled in the art at the time the instant invention was made to modify the invention of Siden by substituting the Me3-psoralen with biotinlayted-psoralen (BPsor) for in situ detection of DNA. Furthermore, one would have a reasonable expectation of success because the use of biotin-avidin system for intra cellular detection of target moieties has been routine in the art at time the instant invention was made. Chevalier et al clearly provides an over all review of an in situ hybridization (ISH) techniques, suggesting that biotin-avidin conjugate can be used for the detection of tissue or cells containing DNA of interest using biotinylated probes (see Fig. 4-6). In addition Chevalier teaches the use of permeabilization of cells or tissue section using permeation-promoting agent, which further facilitate the use of biotin-avidin probes.

The examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law (**See MPEP 2144**).

Thus the invention as claimed is prima facie obvious in view of cited prior art of record.

Conclusion

No claims are allowed.

This is a RCE of applicant's earlier Application No. 10699852. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547.** For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**

SUMESH KAUSHAL
PRIMARY EXAMINER
ART UNIT 1633